SPHERICAL AGGLOMERATION OF BENZOIC ACID USING MEMBRANE EMULSIFICATION

I. Lackowska, M. Dragosavac, B. Benyahia*

[1] Loughborough University; Epinal Way LE11 3TU; Loughborough / United Kingdom
b.benyahia@lboro.ac.uk

ABSTRACT

Spherical agglomeration (SA) is a key crystal shape modification technique commonly used to improve processability and physical properties of active pharmaceutical ingredients (APIs), such as flowability and dissolution. SA involves the introduction of a bridging liquid in the form of droplets into a suspension of API crystals. A novel approach was successfully implemented in this study by adopting a membrane emulsification (ME) system to control the size of bridging liquid droplets and spherical agglomerates. The study investigated ways to achieve the critical quality attributes of the spherical agglomerates by varying operating conditions and design parameters, including mixing rate, bridging liquid injection rate and membrane pore diameter. Antisolvent crystallization of benzoic acid in ethanol (solvent) and water (antisolvent) in presence of toluene as a bridging liquid was used as a case study. Spherical agglomerates of benzoic acid with enhanced quality attributes and mean size of 300 µm were obtained using a membrane pore size of 18 µm, a bridging liquid flow rate of 0.025 mL/min and mixing rate in the range of 800 RPM and 1000 RPM.

Keywords: spherical agglomeration, membrane emulsification, droplet size, benzoic acid

INTRODUCTION

Crystallization is widely adopted in the pharmaceutical industry to purify active pharmaceutical ingredients. In crystallization, the most important challenges are the control of crystal size and shape distributions, polymorphism, and purity. These properties significantly impact the critical quality attributes of the drug product, such as solubility and efficacy, as well as the downstream processability of the resulting crystals such as flowability and filterability (Fysikopoulos et al., 2019). Compared to cuboid and spherical crystals, handling needle-like and plate-like crystals is very challenging due to their very poor flowability and filterability and tendency to break during operation. Several techniques have been developed to modify the crystal shape and aspect ratio including wet milling (Lo et al., 2012), shape additives (Hatcher et al., 2020; Fysikopoulos et al., 2019), layer crystallization (Zhou et al., 2013) and spherical agglomeration (SA) (Orlewski et al., 2018; Peña et al., 2019).

SA is an important shape modification technique which may reduce the number of unit operation and processing steps commonly adopted in the pharmaceutical industry by eliminating processes such as wet granulation. SA is essentially achieved by adding an appropriate bridging liquid at a specific ratio with respect to the mass of crystals, high enough to wet the particles and control the agglomeration process. An effective way to achieve this objective is add the bridging liquid in the form of droplets. Depending on the droplet size of the injected bridging liquid, several mechanisms come into play during the formation of the spherical agglomerates such us adsorption and immersion. The particle size and critical physical properties of the spherical agglomerates are determined by the droplet size distribution of the bridging liquid, mixing conditions and the level of supersaturation. However, the control of the droplet size distribution may be a very challenging task particularly at large scale.

In this work, we propose a novel SA approach based on a membrane emulsification system (Holdich et al., 2010) to effectively control the droplet size distribution of the bridging liquid which in turn can help enhance the critical quality attributes of the spherical agglomerates. Membrane emulsification is a membrane-assisted dispersion process used to generate emulsions of one liquid phase in another immiscible liquid phase, commonly used for oil and water emulsions. It is demonstrated that the membrane pore size widely affects the size and dispersity of the droplets formed. Membrane emulsification systems can be found in many configurations. The one used in this paper employs a dispersion cell with a glass chamber and a nickel

https://doi.org/10.24355/dbbs.084-202110251313-0

membrane at the bottom, where the dispersed phase can be injected through.

The objective of this study is to enhance the critical quality attributes of the spherical agglomerates of benzoic acid by optimizing the critical process parameters (i.e., operating conditions and design parameters) of a fed-batch membrane emulsification system. To achieve this objective, an experimental investigation was conducted to analyze the impact of the bridging liquid flow rate, mixing rate, and membrane pore size on the droplet size and consequently of the size distribution of the spherical agglomerates. In addition, a mathematical model was used to predict the mean droplet size, under the investigated operating conditions, and its impact on the measured mean size of the spherical agglomerates.

RESEARCH CONCEPT

Materials and Methods: A dispersion cell, supplied with a glass chamber holder and a two-blade paddle stirrer, which can hold a flat disc nickel membrane with a pore radius was used, $d_p = 18\ \mu m$ and $33\ \mu m$. Anti-solvent crystallization was performed using 30 wt% benzoic acid (Sigma Aldrich) dissolved in 99.8% ethanol (Fisher Chemical) as the solvent, with deionized water as the antisolvent. Toluene (Fisher Chemical) was used as bridging liquid, to form droplets through the membrane, which would allow for the spherical agglomerates to form. A bridging liquid to API solid weigh ratio (BSR) of 0.7 was used. The crystals were observed under an optical microscope (Nikon Eclipse E100) and fluorescent (Nikon Eclipse TE300) off-line at the end of each crystallization and agglomeration experiment. Agglomerate size was analyzed and measured from optical images using ImageJ.

The spherical agglomeration was achieved in three main steps as shown in Figure 1. Firstly, the crystals were formed using an antisolvent crystallization. A solution of 30 wt.% benzoic acid dissolved in ethanol was added to 36 mL of water present in the dispersion cell to create supersaturation conditions. Once crystals were formed and the system reached equilibrium, the bridging liquid was fed into the system through the membrane forming droplets which initiated the agglomeration process. In the last step, the spherical agglomerates continued to form and grow in absence of any new bridging liquid droplets. Benzoic acid crystals obtained at the end of the crystallization step exhibited mainly needle-like shapes.

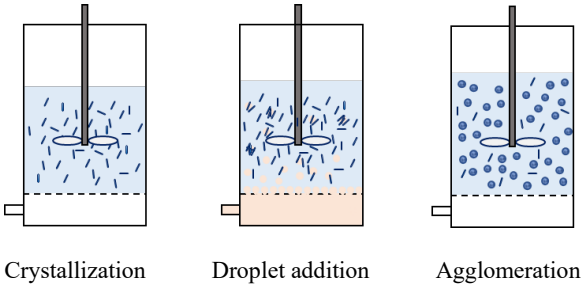

Figure 1: Spherical agglomeration steps

RESULTS AND DISCUSSION

Figure 2 shows the mean size of the bridging liquid droplets as a function of shear stress (mixing conditions) for 2 different membrane pore sizes predicted by a mathematical model which is not presented here for the sake of brevity. This clearly shows that the droplet size decreases as the shear stress increases, and smaller droplets can be obtained with smaller membrane pore sizes. Most importantly, the size of the spherical agglomerates obtained at different bridging liquid flow rates indicate that smaller spherical agglomerates were obtained, as the droplet size decreases then tends to reach a minimum value. To gain better insights, it is important to analyze the size distribution of the spherical agglomerates of benzoic acid. The agglomerate size distribution (ASD) is represented in Figure 3 at three different flow rates of the bridging liquid (Q_{inj}) and at a mixing rate of 800 RPM. Based on these results, smaller mean agglomerate sizes were obtained at lower bridging liquid feed rates (Q_{inj}). In addition, Figure 3 shows that broader size distributions were obtained at high and low bridging liquid feed rates (Q_{inj} = 0.05 mL/min and Q_{inj} = 0.01 mL/min). The best spherical agglomerates were obtained at a medium flowrate Q_{inj} = 0.025 mL/min.

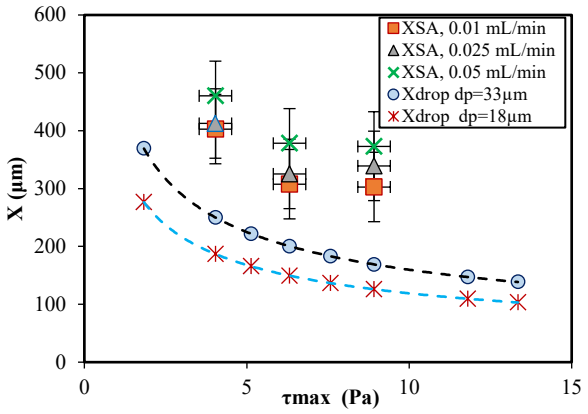

Figure 2: Predicted droplet size at membrane pore diameter d_p=18 and 33µm as a function of shear stress and corresponding measured mean diameter of agglomerates.

https://doi.org/10.24355/dbbs.084-202110251313-0

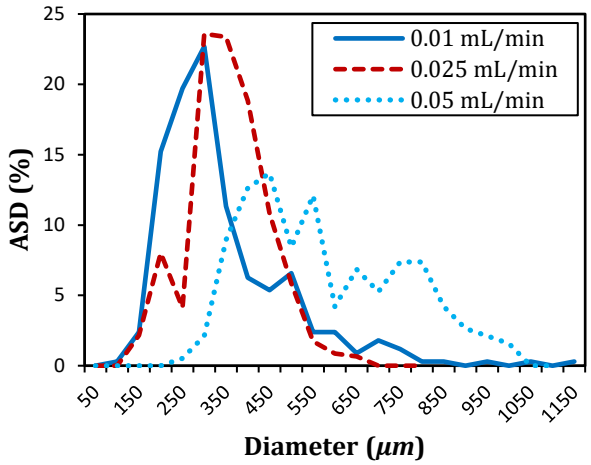

Figure 3: Agglomerate size distribution (ASD) of spherical agglomerates formed at varying Q_{inj} and 800 RPM, nickel membrane, d_p = 33μm.

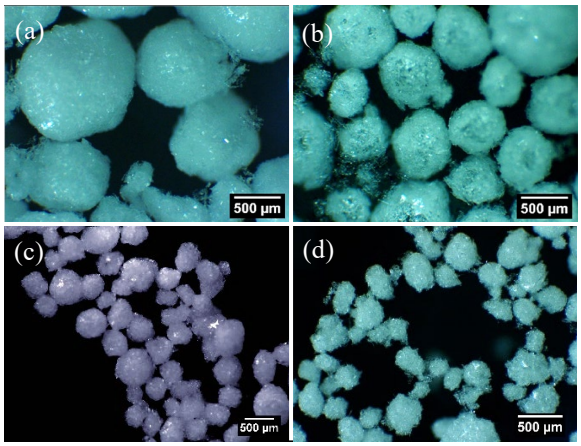

Figure 4: Optical microscopy of the spherical agglomerates of benzoic acid obtained at Q_{inj} = 0.025 mL/min and (a) 600 RPM, d_p = 33μm (b) 800 RPM, d_p = 33μm (c) 1000 RPM, d_p = 33μm (d) 1000 RPM, d_p = 18μm.

Figure 4 shows the optical microscopy of the spherical agglomerates obtained at the same bridging liquid feed rate of 0.025 mL/min at different mixing rates with 2 different membrane pore diameters. The first three images (a-c) represent the spherical agglomerates obtained using a membrane with d_p = 33 μm at different mixing rates, and (d) the spherical agglomerates with a membrane of d_p = 18 μm at 1000 RPM. These results show that large agglomerates with large size distribution are obtained at a lower mixing rate. The best spherical agglomerates were obtained under a mixing rate of 800 RPM and 1000 RPM, under the same Q_{inj} = 0.025 mL/min and using the same membrane pore size. Although the spherical agglomerates obtained under a high mixing rate (1000 RPM) using a small membrane pore size (d_p = 18μm), depicted in Figure 4d, look similar to those obtained under the same mixing rate but with a larger pore size (Figure 4c), the shape distribution and sphericity is enhanced in the latter case.

As no surfactant was added, it was not possible to stabilize and measure off-line the actual size of droplets formed at the membrane surface. The presence of surfactant would allow the formation of more stable small droplets which could result in smaller spherical agglomerates. However, the presence of surfactant may also prevent agglomeration. A process analytical tool such as particle video microscope (PVM) may be employed to measure the size of droplets in real time. However, due to the small size of the dispersion cell, the integration of a PVM probe was not possible. These limitations can be addressed in our future scale-up investigation. Nevertheless, a first principle mathematical model was used to predict the mean droplet size and its influence on the measured properties of the spherical agglomerates.

CONCLUSIONS

Spherical agglomerates of benzoic acid were obtained using a novel approach based on membrane emulsification system. The impact of the operating conditions and design properties were investigated and proved that the system is flexible and suitable to optimize the properties of the spherical agglomerates of benzoic acid. These advantages suggest that the process can be scaled-up reliably which will be the focus of our future work.

The optimization approach was based on both experimental observations and model predictions of the mean size of the bridging liquid droplets. However, a more rigorous modeling approach may be required to predict the properties of the spherical agglomerates.

ACKNOWLEDGMENT

The authors would like to thank the School of AACME, at Loughborough University for funding this project.

REFERENCES

De Luca, G., Di Renzo, A., Di Maio, F.P., et al. (2006) Modelling droplet formation in cross-flow membrane emulsification. *Desalination*, 199 (1–3): 177–179. doi:10.1016/j.desal.2006.03.038.

Egidi, E., Gasparini, G., Holdich, R.G., et al. (2008) Membrane emulsification using membranes of regular pore spacing: Droplet size and uniformity in the presence of surface shear. *Journal of Membrane Science*, 323 (2): 414–420. doi:10.1016/J.MEMSCI.2008.06.047.

Fysikopoulos, D., Benyahia, B., Borsos, A., et al. (2019) A framework for model reliability and estimability analysis of crystallization processes with multi-impurity multi-dimensional population balance models. *Computers & Chemical Engineering*, 122: 275–292. doi:10.1016/J.COMPCHEMENG.2018.09.007.

Hatcher, L.E., Li, W., Payne, P., et al. (2020) Tuning Morphology in Active Pharmaceutical Ingredients: Controlling the Crystal Habit of Lovastatin through Solvent Choice and Non-Size-Matched Polymer Additives. *Crystal Growth & Design*, 20 (9): 5854–5862. doi:10.1021/ACS.CGD.0C00470.

Holdich, R., Dragosavac, M., Williams, B., et al. (2020) High throughput membrane emulsification using a single-pass annular flow crossflow membrane. *AIChE Journal*, 66 (6): 1–10. doi:10.1002/aic.16958.

Holdich, R.G., Dragosavac, M.M., Vladisavljevic, G.T., et al. (2010) Membrane Emulsification with Oscillating and Stationary Membranes. *Industrial & Engineering Chemistry Research*, 49 (8): 3810–3817. doi:10.1021/ie900531n.

Lo, E., Mattas, E., Wei, C., Kacsur, D., Chen, C. K. (2012) Simultaneous API Particle Size Reduction and Polymorph Transformation Using High Shear. *Org. Process Res. Dev.*, *16* (1), 102–108. 10.1021/op2002529

Orlewski, P.M., Ahn, B. and Mazzotti, M. (2018) Tuning the particle sizes in spherical agglomeration. *Crystal Growth and Design*, 18 (10): 6257–6265. doi:10.1021/acs.cgd.8b01134.

Peña, R., Jarmer, D.J., Burcham, C.L., et al. (2019) Further Understanding of Agglomeration Mechanisms in Spherical Crystallization Systems: Benzoic Acid Case Study. *Crystal Growth and Design*, 19 (3): 1668–1679. doi:10.1021/acs.cgd.8b01519.

Zhou, L., Su, M., Benyahia, B., Singh, A., Barton, P.I., Trout, B.L., Myerson, A.S., Braatz, R.D. (2013) Mathematical modeling and design of layer crystallization in a concentric annulus with and without recirculation. AIChE J, 59(4), 1308-1321. doi.org/10.1002/aic.14049

https://doi.org/10.24355/dbbs.084-202110251313-0